NGF homodimer binds to p75NTR

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 70

This document contains 1 reaction (see Table of Contents)
NGF homodimer binds to p75NTR

Stable identifier: R-HSA-193653

Type: binding

Compartments: extracellular region, plasma membrane

p75NTR exists in a multimeric form both in presence or absence of NGF. In the NGF:p75NTR complex, a single p75 molecule is asymmetrically bound to a NGF homodimer, along the homodimeric interface of NGF. This causes an allosteric conformational change, which disables the NGF symmetry-related second p75 binding site. Therefore, it is possible that NGF has to perturb or alter the preformed p75 dimer orientation in order to initiate intracellular signalling. NGF:p75NTR complexes are not so long living as the NGF:TRKA complexes. This is due, at least in part, to the fact that TRKA homodimers are internalized, and continue signalling in endosomes.

Contrary to what is commonly believed, NGF bind to p75NTR and TRKA, individually, with a similar equilibrium binding constant (Kd \~ 1-2 nM). As a matter of fact, the association constant for NGF binding to p75NTR (k+1 = 8x10 to power of 6 M\(^{-1}\) s\(^{-1}\)) is faster than for TRKA (k+1 = 8x10 to power of 5 M\(^{-1}\) s\(^{-1}\)). On the other hand, the off rate of the NGF:TRKA complex (k-1 = 7.2x10 to power of -5 s\(^{-1}\)) is much slower than the NGF:p75NTR complex (k-1 = 1x10 to power of -3 s\(^{-1}\)) . p75NTR and TRK receptors functionally interact, but the precise means by which this occurs has remained unresolved. This could result from a direct physical interaction or be explained by convergent signalling of these two receptors. Co-expression of both p75NTR and TRKA at the cell surface appears to result in the formation of a “high-affinity” binding site that has an accelerated rate of NGF association and a 30- to 100-fold higher affinity for NGF (Kd \~ 1-3 x 10 to power of -11 M) than either receptor alone.

The high-affinity binding sites appear to constitute 10\%–15\% of the total NGF binding sites. The nature of such high affinity binding sites is still unclear. They could be due to a multimeric complex of p75:TRKA proteins. Alternatively, NGF might first rapidly bind to p75NTR and then be presented to TRKA in a conformation that lowers its TRKA association rate. Some authors even question the existence of these high affinity sites. Structural data on NGF complexes with p75NTR and TRKA extracellular domains suggest that formation of a ternary complex TRKA:NGF:p75NTR in a 1:2:1 ration is theoretically possible, although unlikely. However, biochemical data so far failed to show that this complex forms.

Literature references


## Editions

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